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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/693,754	10/20/2000	Neil Berinstein	13115	7885

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AVENTIS PASTEUR
DISCOVERY DRIVE
SWIFTWATER, PA 18370

EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/693,754	BERINSTEIN ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/17/04 has been entered. Applicant's amendment filed on 6/17/04 has also been entered. Claim 28 has been canceled. Claims 1-2, and 4-27 are pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in the instant action can be found in the previous office action.

Claim Rejections - 35 USC § 103

The rejection of claims 1-2, 4-17, and 20 under 35 U.S.C. 103(a) as being unpatentable over Hurpin et al. (1998) Vaccine, Vol. 16 (2/3) 208-215, in view of Hodge et al. (1997) Vaccine, Vol. 15, No. 6/7, 759-768, and Lehner et al. (1999) J. Infect. Dis., Vol. 179 (Suppl 3), S489-S492, is withdrawn in view of applicant's amendments to the claims to recite direct administration into a lymph node.

The rejection of claims 18-19 under 35 U.S.C. 103(a) as being unpatentable over Hurpin et al. (1998) Vaccine, Vol. 16 (2/3) 208-215, in view of Hodge et al. (1997) Vaccine, Vol. 15, No. 6/7, 759-768, and Lehner et al. (1999) J. Infect. Dis., Vol. 179 (Suppl 3), S489-S492, as applied to claims 1-2, 4-17, and 20 above, and further in view of Zaremba et al. (1997) Canc. Res., Vol. 57, 4570-4577 and Salgaller et al. (1996) Canc. Res., Vol. 56, 4749-4757, is withdrawn in view of applicant's amendments to the claims to recite direct administration into a lymph node.

The rejection of claims 21-28 under 35 U.S.C. 103(a) as being unpatentable over Hurpin et al. (1998) Vaccine, Vol. 16 (2/3) 208-215, in view of Hodge et al. (1997) Vaccine, Vol. 15, No. 6/7, 759-768, and Lehner et al. (1999) J. Infect. Dis., Vol. 179 (Suppl 3), S489-S492, as applied to claims 1-2, 4-17, and 20 above, and further in view of Barnett et al. (1997) Vaccine, Vol. 15(8), 869-873, is withdrawn in view of applicant's amendments to the claims to recite direct administration into a lymph node.

Applicant's amendments to the claims have resulted in the following new grounds of rejection.

Claims 1-2, 4-17, and 20 under 35 U.S.C. 103(a) as being unpatentable over Hurpin et al. (1998) Vaccine, Vol. 16 (2/3) 208-215, in view of Hodge et al. (1997) Vaccine, Vol. 15, No. 6/7, 759-768, US 2003/0022854 (2003) Dow et al., and Lehner et al. (1999) J. Infect. Dis., Vol. 179 (Suppl 3), S489-S492. The applicant claims methods of inducing an immune response to a tumor

antigen in an animal comprising a priming step wherein a tumor antigen is administered in a first form to a lymphatic site, and a boosting step wherein the tumor antigen is administered in a second form to a lymphatic site, wherein at least one or both of said forms is administered directly into a lymph node. The applicant further claims said methods wherein the tumor antigen is selected from a group which includes p53 and wherein the tumor antigen is in the form of a nucleic acid selected from a group which includes the canarypox nucleic acid, ALVAC.

Hurpin et al. teaches the generation of anti-53 CTL responses in mice following intrasplenic injection of ALVAC encoding p53 (Hurpin et al., page 209, column 2, second paragraph, and page 210, column 2, last paragraph, and page 211, Figure 1, panel b). While Hurpin et al. does not specifically teach a boosting step in addition to a priming step, Hurpin et al. does teach that the route of administration is also important for boosting the response (Hurpin et al., page 211, column 1, paragraph 1). Hodge et al. supplements Hurpin et al. by teaching a diversified prime and boost protocol for enhancing T-cell immunity and antitumor immune responses. Specifically, Hodge et al. teaches that priming an anti-tumor immune response by administering a vaccinia virus encoding CEA followed by boosting with an avipox virus (ALVAC) encoding CEA results in the generation of anti-CEA immune responses superior to those generated by the use of either vector alone (Hodge et al., page 759, and page 766, Table 3). Please note that Vaccinia virus encoding CEA and ALVAC encoding CEA represent different forms of the same tumor antigen since vaccinia is a cowpox virus and ALVAC is an avipox virus.

While Hurpin et al. teaches the administration of the tumor antigen to a lymphatic site, the spleen, neither Hurpin et al. nor Hodge et al. specifically teaches the administration of the

antigen to the lymph node or directly into the lymph node. Dow et al. supplements Hurpin et al. and Hodge et al. by teaching that many routes of administration can be used to administer protein or nucleic acid tumor antigen to a mammal in order to induce an immune response, one preferable route being intranodal administration (Dow et al., page 13, column 2, and pages 20-21). Lehner et al. further supplements Hurpin et al., Hodge et al., and Dow et al. by providing motivation for targeting antigen to lymph nodes. Lehner et al. teaches that the route of administration can have profound effects on the immune response. Specifically, Lehner et al. showed that a direct comparison of intramuscular versus intradermal versus targeted iliac lymph node immunization revealed that targeted iliac lymph node administration of antigen resulted in increased T and B cell mediated antigen-specific immune responses (Lehner et al., page S489, and page S491). Thus, by demonstrating that administration of antigen to the iliac lymph node results in increased T and B cell mediated antigen-specific immune responses over other routes of administration, Lehner et al. provides motivation for substituting intranodal administration as taught by Dow et al. over the intrasplenic or intramuscular administration routes taught by Hurpin et al. and Hodge et al.

Based on the motivation to use a diversified prime and boost strategy as taught by Hodge et al., the motivation to utilize lymphatic administration for generating CTL using ALVAC encoding tumor antigens as taught by Hurpin et al., the motivation to specifically target iliac lymph node to maximize immune responses as taught by Lehner et al., and the teachings of Dow et al. that intranodal administration is a preferred route for immunizing with tumor antigen, it would have been *prima facie* obvious to the skilled artisan at the time of filing to administer a vaccinia virus encoding a tumor antigen, either CEA or p53, directly to a lymphatic site using

intranodal administration, followed by the intrasplenic or intranodal administration of an avipox vector encoding either CEA or p53 in order to induce an immune response in an animal. Further, based on the successful use of intrasplenic and intranodal administration to generate antigen specific T and B cell responses as taught by Hurpin et al., Dow et al., and Lehner et al., and the successful use of a second vector to boost the immune response taught by Hodge, the skilled artisan would have had a reasonable expectation of success in inducing an immune response in an animal by direct intranodal administration of a vaccinia virus encoding a tumor antigen, either CEA or p53, followed by the intranodal administration of an avipox vector encoding either CEA or p53.

Applicant's arguments concerning the teachings of Hurpin et al., Hodge et al., and Lehner et al. have been addressed as they pertain to the instant grounds of rejection. The applicant argues that the claims have been amended to recite the direct administration of the immunogen into a lymph node and that none of Hurpin et al. , Hodge et al. , or Lehner et al. teach direct administration into the lymph node. In particular, the applicant argues that Lehner et al. teaches the subcutaneous administration of immunogen in the proximity of the iliac lymph nodes rather than direct administration to the lymph node. However, in the instant rejection of record, the teachings of Dow et al. have been added. Dow et al. does in fact teach intranodal administration of tumor antigen, not subcutaneous administration in the vicinity of the lymph node. Lehner et al. continues to be relied on for motivation to motivation to target immunogen to the lymph node. Therefore, applicant's arguments regarding the teachings of Hurpin et al., Hodge et al., and Lehner et al., have not been found persuasive in overcoming the instant grounds of rejection of

the claims based on the combined teachings of Hurpin et al., Hodge et al., Dow et al., and Lehner et al..

Claims 18-19 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Hurpin et al. (1998) Vaccine, Vol. 16 (2/3) 208-215, in view of Hodge et al. (1997) Vaccine, Vol. 15, No. 6/7, 759-768, US 2003/0022854 (2003) Dow et al., and Lehner et al. (1999) J. Infect. Dis., Vol. 179 (Suppl 3), S489-S492, as applied to claims 1-2, 4-17, and 20 above, and further in view of Zaremba et al. (1997) Canc. Res., Vol. 57, 4570-4577 and Salgaller et al. (1996) Canc. Res., Vol. 56, 4749-4757. The applicant claims methods of inducing an immune response to a tumor antigen in an animal comprising a priming step wherein a tumor antigen is administered in a first form directly into a lymphatic site, and a boosting step wherein the tumor antigen is administered in a second form to a lymphatic site, wherein either one or both of the lymphatic sites is a lymph node. The applicant further claims said methods wherein the tumor antigen comprises the sequence YLSGADLNL or YLEPGPVTV.

The combined teachings of Hurpin et al. in view of Hodge et al. , Dow et al., and Lehner et al., as discussed in detail above, provide motivation for the use of a diversified prime and boost strategy which utilizes direct intranodal injection of a vaccinia virus encoding a tumor antigen, such as CEA or p53, followed by the intranodal administration of an avipox vector encoding a tumor antigen in order to induce an immune response in an animal. While Hurpin et al., Hodge et al., and Dow et al. teach the generation of anti-tumor immune responses against tumor antigens, including CEA, neither Hurpin et al. nor Hodge et al. teach wherein the tumor antigen comprises the sequence YLSGADLNL or YLEPGPVTV.

Zaremba et al. supplies the missing teaching by demonstrating that the YLSGADLNL epitope is a CTL enhancer agonist peptide for inducing potent anti-CEA CTL (Zaremba et al., page 4570, abstract). Zaremba et al. further provides motivation for using the modified CEA peptide to induce anti-CEA CTL by teaching that the YLSGADLNL peptide is more potent that the unmodified YLSGANLNL peptide in inducing anti-CEA CTL (Zaremba et al., page 4574). Sangeller et al. further supplements Hurpin and Hodge by teaching a modified gp100 peptide YLEPGPVTV, which also demonstrates an enhanced ability to generate anti-gp100 CTL than the unmodified YLEPGPVTA peptide (Sangeller et al., page 4749, abstract and column 2). Thus, based on the motivation provided by Zaremba et al. and Sangeller et al. that the modified peptides YLSGADLNL and YLEPGPVTV are more potent than the unmodified parent peptides at generating anti-CEA or anti-gp100 CTL respectively, it would have been *prima facie* obvious to the skilled artisan at the time of filing to substitute the modified YLSGADLNL or YLEPGPVTV peptides for the unmodified tumor antigens taught by Hurpin and Hodge, and further to use those peptides in the methods of Hurpin et al. in view of Hodge et al., Dow et al., and Lehner et al. for immunizing a mammal with a reasonable expectation of success.

Applicant's arguments concerning the teachings of Hurpin et al., Hodge et al., and Lehner et al. have been addressed in detail above and have not been found persuasive in view of the teachings of Dow et al.

Claims 21-28 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Hurpin et al. (1998) Vaccine, Vol. 16 (2/3) 208-215, in view of Hodge et al. (1997) Vaccine, Vol. 15, No. 6/7, 759-768, US 2003/0022854 (2003) Dow et al., and Lehner et al. (1999) J.

Infect. Dis., Vol. 179 (Suppl 3), S489-S492, as applied to claims 1-2, 4-17, and 20 above, and further in view of Barnett et al. (1997) Vaccine, Vol. 15(8), 869-873. The applicant claims methods of inducing an immune response to a tumor antigen in an animal comprising a priming step wherein a tumor antigen is administered in a first form directly to a lymphatic site, and a boosting step wherein the tumor antigen is administered in a second form to a lymphatic site, wherein either one or both of the lymphatic sites is a lymph node. The applicant further claims said methods wherein the first form is a nucleic acid and the second form in a peptide.

The combined teachings of Hurpin et al. in view of Hodge et al., Dow et al., and Lehner et al., as discussed in detail above, provide motivation for the use of a diversified prime and boost strategy which utilizes direct intranodal injection of a vaccinia virus encoding a tumor antigen, such as CEA or p53, followed by the intranodal administration of an avipox vector encoding a tumor antigen in order to induce an immune response in an animal. Although Hurpin et al. and Hodge et al. teach immunization using a nucleic acid encoding the tumor antigen in the form of a recombinant virus, neither reference teaches boosting the immune response from a nucleic acid immunization with a peptide.

Barnett et al. supplements Hurpin et al., Hodge et al., Dow et al., and Lehner et al., by teaching a prime/boost vaccination strategy which includes a priming step with a nucleic acid encoding an antigen and a boosting step with a protein form of the antigen (Barnett et al., page 869-870). Barnett et al. also teaches that the nucleic acid form of the antigen can be a plasmid DNA vector or recombinant canarypox virus (Barnett et al., page 869, and page 872, column 2, last paragraph). Barnett et al. further provides motivation for including a boosting immunization with polypeptide antigen following recombinant nucleic acid immunization by demonstrating

that animals vaccinated using the prime/boost strategy had significantly increase T and B cell responses than animals which received the nucleic acid alone (Barnett et al., page 869, and page 871).

Therefore, based on the motivation for boosting nucleic acid based immunization with the administration of polypeptide antigen provided by Barnett et al., and in view of the motivation provided by Hodge et al. for prime/boost immunization using two different recombinant viruses, it would have been *prima facie* obvious at the time of filing to use utilize the prime/boost strategy of either Hodge et al. or Barnett et al. in order to increase antigen specific T and B cell responses in an animal. Further, based on the successful demonstration by Barnett et al. that boosting with polypeptide antigen increases antigen specific immune responses, the skilled artisan would have had a reasonable expectation of success in generating anti-tumor antigen specific immune responses *in vivo* by priming with a nucleic acid such as a plasmid or recombinant canarypox virus encoding a tumor antigen and boosting with a polypeptide form of the antigen.

Applicant's arguments concerning the teachings of Hurpin et al., Hodge et al., and Lehner et al. have been addressed in detail above and have not been found persuasive in view of the teachings of Dow et al.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be

reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER